Erythrophagocytosis induced ferroptosis contribute to pulmonary microvascular thrombosis and thrombotic vascular remodeling in pulmonary arterial hypertension

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Abstract

Background: Whether primary or just as a complication from the progression of pulmonary arterial hypertension (PAH), thrombosis seems to be an important player in this condition. The cross-talk between red blood cells (RBCs) and pulmonary microvascular endothelial cells (PMVECs) and their role in PAH remain undefined.

Objectives: The goals of this study were to assess the role of RBC-PMVEC interaction in microvascular thrombosis and thrombotic vascular remodeling under hypoxic conditions.

Methods: We established an in vitro hypoxic co-incubation model of RBC and PMVEC as well as a hypoxic mice model. We investigated erythrophagocytosis (EP), ferroptosis, thrombosis tendency, and pulmonary hemodynamics in experimental PAH.

Results: We showed that increased EP in PMVEC triggered ferroptosis, enhanced procoagulant activity, and exacerbated vessel remodeling under hypoxic conditions. In the PAH mice model induced by chronic hypoxia, EP-induced ferroptosis followed by upregulated TMEM16F led to a high tendency of thrombus formation and thrombotic vascular remodeling. Inhibition of ferroptosis or silence of TMEM16F could alleviate hypercoagulable phenotype, reverse right ventricular (RV) systolic pressure, RV hypertrophy index, and remodeling of pulmonary vessels.

Conclusions: These results illustrate the pathogenic RBC–PMVEC interactions in PAH. Inhibition EP, ferroptosis, or TMEM16F could be a novel therapeutic target to prevent PAH development and thrombotic complications.

Key words: erythrophagocytosis; ferroptosis; thrombosis; pulmonary arterial hypertension; TMEM16F